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CYCLIC ACETALS OF KETOSES

PART IV*. RE-INVESTIGATION OF THE OXIDATION OF 1,2:4,5-DI-*O*-ISOPROPYLIDENE-β-D-FRUCTOPYRANOSE WITH METHYL SULFOXIDE–ACETIC ANHYDRIDE

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ABSTRACT

For the preparation of pure D-psicose (**5a**) via oxidation of 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**2a**), the latter must be free from its 2,3:4,5 isomer (**6a**), which is oxidized to the corresponding aldosulose acetal. Pure 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulo-2,6-pyranose (**3**) undergoes stereospecific reduction with sodium borohydride to give only 1,2:4,5-di-*O*-isopropylidene-β-D-*ribo*-hexulopyranose (**4a**), which exists as two different crystal modifications. Compounds **3** and **4a** have been characterized, and discrepancies in the literature have been explained.

INTRODUCTION

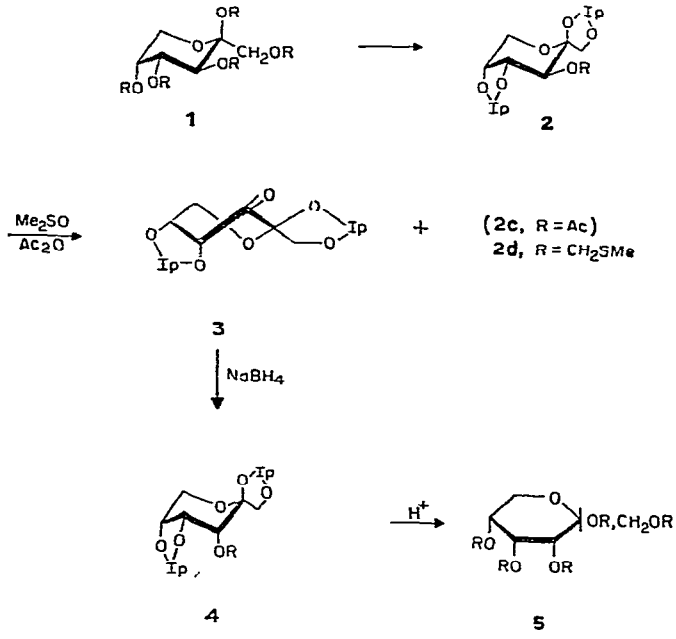
A crystalline derivative of D-psicose was desired for issuance by the National Bureau of Standards as a Standard Reference Material. We have therefore had occasion to synthesize fairly large quantities of the sugar, and have, in particular, re-investigated the preparation of its 1,2:4,5-di-*O*-isopropylidene derivative.

D-Psicose (D-*ribo*-hexulose, **5a**) is a rare sugar that occurs in the antibiotic psicofuranine[4] (9-β-D-psicofuranosyladenine) and in *Itea* plants[5]; it has also been found in the nonfermentable fraction of cane molasses[6], where it may have been formed by the action of the lime used in sugar manufacture. D-Psicose was first synthesized[7] in 1936, by the pyridine-catalyzed isomerization of D-allose; it has also been prepared by a 6-step synthesis[8] from D-ribose, by a 4-step synthesis[9] from D-fructose, by mild isomerization of D-glucose with alkali[10], and by isomerization of D-fructose by *N,N'*-dicyclohexylcarbodiimide in hot methanol[11] to D-psicose, D-glucose, and D-mannose, followed by fermentation with bakers' yeast. However, some of these methods require expensive starting-materials, and all of them are tedious and give low overall yields.

In 1967, McDonald[12] described a new synthesis of the sugar, starting from D-fructose (**1a**), that involved the following steps. Compound **1a** was converted into 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**2a**), and this was oxidized with methyl sulfoxide–acetic anhydride (oxidant I) to 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulo-2,6-pyranose (**3**); it was stated that the 3-acetate (**2c**) of com-

*For previous papers in this series, see Refs. 1–3.

pound **2a** was simultaneously formed, but that recrystallization of the crude product afforded pure **3**. Reduction of **3** with sodium borohydride in aqueous methanol then gave 1,2:4,5-di-*O*-isopropylidene-β-D-*ribo*-hexulopyranose (**4a**) contaminated with "only a trace" of the corresponding D-fructose diacetal (**2a***), presumably removed on recrystallization of the crude **4a**; and acid hydrolysis of compound **4a** afforded D-psicose (**5a**).



a, R=H

b, R=$SiMe_3$

Because this synthesis provides a direct means for preparing D-psicose, it was decided to repeat this procedure to produce a supply of the crystalline 1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranose (**4a**) for use as a Standard Reference Material. Three months after publication of McDonald's Note[12], a more detailed article describing similar work was published independently[14]; certain of the conclusions described in the latter article had been arrived at by us[15]. Finally, in 1968, another article was published on the same subject[16]. The present article is published in order to explain certain discrepancies between the results of the three sets of workers[12,14,16].

RESULTS AND DISCUSSION

In our study, McDonald's procedure[12] for preparing **3** was first repeated in accordance with her instructions. Compound **2a** was oxidized during 24 h at 25° with a solution of acetic anhydride (1 molar proportion) in methyl sulfoxide (70 molar

*Takagi and Rosenstein[13] have found that, in crystalline **2a**, the conformation of the molecules is intermediate between *IC* (D) and H_0^2 (D).

proportions), and crude compound **3** was isolated in a yield of ~50% of the theoretical, as compared with the 70% yield of crude product reported by McDonald[12]. Because of this result, a series of experiments was performed in which the molar proportions of **2a** to acetic anhydride (A) to methyl sulfoxide (B) were 1:2:42, 1:16:42, and 1:21:42, but the yield of **3** (recrystallized) was only raised to 52–54% of the theoretical. As the oxidation of 1 mole of **2a** with McDonald's proportions would require the use of 5 liters of methyl sulfoxide, the molar proportions of **2a**:A:B were changed to 1:10:10, in contrast to the ratios of 1:1:70 (Ref. 12), 1:23:46 (Ref. 14), and 1:43:85 (Ref. 16) reported in the literature. The reaction was monitored by t.l.c. on Silica Gel G, and we found that (*a*) the time necessary for completion of the reaction with the 1:10:10 ratios was 4 days, as compared with 2 days[12] and 1 day[14,16]; and (*b*) only two products are formed. James and co-workers[14] reported that *three* products are formed, whereas the other workers[12,16] found only two.

In all of these experiments, we found that, accompanying compound **3**, there was a large proportion of a different crystalline compound (X) that, solely on the basis of R_F values in t.l.c., had been regarded by McDonald[12] as being the 3-acetate **2c**. (The rather close R_F values of X and **2c** in her solvent system explain the misidentification.) However, we found that the second product (X) shows no carbonyl absorption in its i.r. spectrum, and therefore could not be the acetate **2c**. To verify this conclusion, we prepared an authentic specimen of acetate **2c** by the method of Fischer and Noth[17], and found that the i.r. spectrum of **2c**, which shows bands at 1735 (C=O) and 1240 cm^{-1} (C–O), is entirely different from that of compound X. A mixture of compound X (m.p. 82.5–83°) with compound **2c** (m.p. 76–77°) melted at 59°. Compound X was identified[14] as **2d**, the 3-(methylthio)methyl ether of compound **2a**.

To effect separation of the diulose acetal **3** from X (**2d**), McDonald[12] recrystallized the crude product from methanol, to afford **3**; compound **2d** was not recovered. James and co-workers[14] isolated **3** by recrystallization of the crude product from petroleum ether; the mother liquor was evaporated to dryness and the resulting syrup was crystallized from petroleum ether to give a mixture of crystalline **3** (as needles) and **2d** (as rectangular plates). These were separated "mechanically", and recrystallization of the platelets from petroleum ether gave **2d**. We have found that the two compounds are readily separated by dissolution of the mixture in absolute methanol (5 ml/g) and addition of water (2.5 ml/g); the ether **2d** crystallizes out almost quantitatively and is filtered off, and the mother liquor is evaporated to dryness and the residue crystallized from hexane to give **3**.

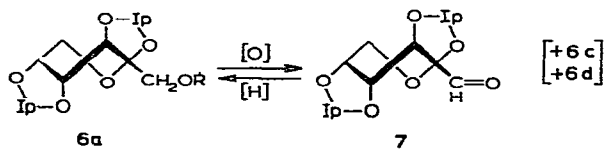
Whereas the diulose acetal **3** has been reported to have $[\alpha]_D$ −100.4° (in acetone[12]), −126.4° (in chloroform[14]), and −106° (in ethanol[16]), we found $[\alpha]_D^{25}$ −104.7° (in acetone), −119.2° (in chloroform), and −113.5° (in ethanol). Because of these discrepancies, we decided to prepare compound **3** by oxidation of **2a** with ruthenium tetraoxide[16] (oxidant II) by an improved procedure[18]. In this way, **3** was obtained that was homogeneous by t.l.c and g.l.c. analysis; it had the same specific rotations as those we had found for **3** prepared by use of oxidant I.

The reduction of pure compound **3** (prepared by use of either oxidant) was effected with sodium borohydride by a modification of the procedure of James and co-workers[14]. G.l.c. analysis of the 3-(trimethylsilyl) ether (**4b**) of the "crude" crystalline product, under conditions that would have detected the presence of 0.1% (or more) of compound **2b**, revealed that the product consisted solely of **4a**. Hence, the reduction is completely stereospecific.

This result is not in agreement with that of the earlier workers. By t.l.c., McDonald[12] found "a trace" of **2a** in the product obtained on reduction of **3** (prepared with oxidant I) with sodium borohydride. Cree and Perlin[16] reported that, on reduction of **3** (prepared with oxidant II) with lithium aluminium hydride, "only a trace of the D-fructose derivative was formed during the reduction, and sodium borohydride in aqueous ethanol was *almost* as exclusively selective in favoring the production" of **4a**. In contrast, on reduction of **3** prepared with oxidant I, James *et al.*[14] found, by g.l.c. analysis, 10% of **2a** in crude **4a** obtained by reduction with lithium aluminum hydride, and 1.8% of **2a** when **3** was reduced with sodium borohydride.

We have sought an explanation for these discrepancies. The possibility that **2a**, as a contaminant of **4a**, arose from **2d** as a contaminant of **3** was excluded, as we found that **2d** is unaffected by sodium borohydride under the conditions used for reducing **3** to **4a**. Hence, the only explanation possible is that a small proportion of **2a** remained unchanged on oxidation of **2a**, and that it was carried as a contaminant of **3** (and, thence, of **4a**); the presence of a small proportion of **2a** in **3** would not be readily revealed by the t.l.c. procedures that had been used[12,14,16].

In addition to **3** and **2d**, James *et al.*[14] found, in the mixture obtained by treating **2a** with oxidant I for 1 day, a third component that was not unoxidized **2a**. It has been established[3] that many commercial and laboratory samples of **2a** are contaminated with 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**6a**). We have now found that, on treatment with oxidant I under the conditions that we had used for oxidation of **2a**, compound **6a** is converted into a mixture of 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hexosulo-2,6-pyranose (**7**) and two other products [presumably the 1-acetate (**6c**) and 1-(methylthio)methyl ether (**6d**) of **6a**]. In the t.l.c. developer used by James *et al*[14], compound **7** has R_F 0.39, and the mixture of compounds **6c** and **6d** has R_F 0.72; the latter is the R_F value reported[14] for the "third



6a 7

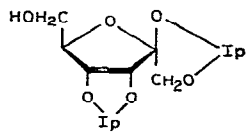
a R = H
b R = $SiMe_3$
c R = Ac
d R = CH_2SMe

product" detected in the oxidation of **2a** by oxidant I, showing that their **2a** might, indeed, have been contaminated with **6a**. The presence of a small proportion of **6a** in **2a** would not be readily revealed by the t.l.c. procedures that had been used[12,14,16].

Reduction of compound **7**, under the conditions that we had used for the reduction of compound **3**, afforded compound **6a**. Thus, if **6a** is a contaminant of **2a**, it will give its oxidation product (**7**) as a contaminant of **3**; on reduction of this mixture, **6a** will be a contaminant of **4a**, and thence, D-fructose (**1a**) will be a contaminant of the desired D-psicose (**5a**). We therefore emphasize that, for preparation of pure **4a**, the diacetal **2a** used as the starting material must be free from diacetal **6a**, and, before reduction, the diulose acetal **3** must be free from **2a**.

Such contamination of **4a** by **2a** or **6a** is most readily detected by hydrolysis of **4a** to **5a**, because **5a** has[8] $[\alpha]_D$ +4.7° (in water), whereas **1a** (from any **2a** or **6a** present as a contaminant) has[19] $[\alpha]_D$ −92° (water). On hydrolysis of our samples of **4a** with 0.1M oxalic acid at 65°, the resulting solution of **5a** had $[\alpha]_D$ +4.7° (in water) and the sugar was homogeneous by t.l.c.[1] and by g.l.c. of its per-*O*-(trimethylsilyl) derivative (**5b**). The previous workers[12,14,16] did not report having applied these tests to their samples of **4a**.

Freshly recrystallized **4a** had m.p. 68–69° and $[\alpha]_D^{25}$ −116.4° (in acetone), but, after it had been kept for several months at room temperature, the m.p. was 56–58°. This change has been observed before[14], and cited as evidence for a supposed rearrangement of crystalline **4a** to crystalline 1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose (**8**); however, we found that the change in m.p. of **4a** was unaccompanied



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by any change in R_F value, X-ray powder diffraction pattern, i.r. spectrum (both of the solid and in solution in chloroform, with solvent compensation), or optical rotation, whereas compound **8** has[7] m.p. 57–58.5° and $[\alpha]_D^{20}$ −98.2° (in acetone). Hence, the change in m.p. of **4a** must be ascribable to physical change from an unstable to a stable crystal modification, and not to a chemical change in structure.

EXPERIMENTAL

General methods. — G.l.c. was performed on a Varian Aerograph Model 2100-20* gas chromatograph, by use of glass columns (5 ft × 2 mm i.d.) of 3% of SE-30 on 100–120 mesh VarAport 30 kept at 170°. The flow rate of the nitrogen carrier-gas was 25 ml/min and hydrogen-flame detectors were used. Tri-Sil "Z" [*N*-(trimethyl-

*Certain commercial products and instruments are identified in this paper in order to specify the experimental procedure adequately. In no case does such identification imply recommendation or endorsement by the National Bureau of Standards, nor does it imply that the product or equipment identified is necessarily the best available for the purpose.

silyl)imidazole in pyridine, Pierce Chemical Company, Rockford, Illinois, U.S.A.] was used for preparing the trimethylsilyl derivatives. Retention times and response ratios were determined with authentic samples of **1b**, **2b**, **2d**, **3**, **4b**, **5b**, and **6b**. T.l.c. was performed with Silica Gel G (E. Merck, Darmstadt, Germany), activated at 110°, as the adsorbent; with small plates, 1:3 (v/v) ethyl acetate–pentane (solvent A) was found preferable to 3:1 (v/v) ethyl acetate–petroleum ether[12] (solvent B) as the developing solvent, and, for comparison with the results of James *et al.*[14], 24:1 (v/v) benzene–methanol (solvent C) was also used; indication of zones was effected with sulfuric acid. I.r. spectra were recorded with a Perkin–Elmer Model 257 grating i.r. spectrophotometer. Optical rotations were determined, for solutions in 1-dm tubes, with a Perkin–Elmer Model 141 automatic polarimeter. X-ray powder diffraction data were obtained by use of a General Electric scanning diffractometer equipped with a lithium fluoride monochromator and a Geiger counter for detection, and are given as interplanar spacings, Å, for CuKα radiation. Relative intensities were estimated visually: m, moderate ; s, strong; w, weak. Melting points were determined in a silicone oil-bath, and are uncorrected. Solutions were usually evaporated below 40° under diminished pressure.

*1,2:4,5-Di-*O*-isopropylidene-β-*D*-fructopyranose* (**2a**). — The purity of the D-fructose (**1a**) used was first checked as follows. A suspension of **1a** (D-levulose "Special"; Pfanstiehl Chemical Co., Waukegan, Illinois, U.S.A.) (10 mg) in 1 ml of Tri-Sil "Z" was heated at 60° until the sugar had dissolved (5 min). The resulting solution of **1b** was cooled, and injected directly into the chromatograph; only one peak, having a retention time of 268 sec, was observed.

Compound **2a** was prepared from **1a** by an improved method[3]. Recrystallized from 1:1 (v/v) ether–pentane (10 ml/g), it had m.p. 119°, $[\alpha]_D^{25}$ −154.8° (*c* 1.0, acetone), −145.0° (*c* 1.4, chloroform), −158.0° (*c* 1.1, ethanol); lit.[20] m.p. 119–120°; lit.[21] m.p. 118–119°, $[\alpha]_D^{23}$ −154° (in acetone); lit.[22] m.p. 118–119°, $[\alpha]_D^{20}$ −146.6° (in chloroform). Its i.r. spectrum was identical with that of the authentic compound[23], and g.l.c. analysis of its 3-(trimethylsilyl) ether (**2b**) showed only one peak, having a retention time of 100 sec. On t.l.c., it showed only one component, which had R_F 0.30 (solvent A), 0.75 (solvent B), and 0.24 (solvent C); lit.[14] R_F 0.21 (solvent C).

*3-*O*-Acetyl-1,2:4,5-di-*O*-isopropylidene-β-*D*-fructopyranose* (**2c**). — To a solution of 13.0 g (50 mmoles) of **2a** in dry pyridine (25 ml) was added 6 ml (55 mmoles) of acetic anhydride, and the solution was kept overnight at room temperature. Ice (about 50 g) was added, with stirring, and the resulting solution was extracted with three 50-ml portions of chloroform. The extracts were combined, washed successively with saturated aqueous potassium hydrogen sulfate solution, water, and saturated aqueous sodium hydrogen carbonate solution, dried (anhydrous sodium sulfate), and evaporated to a syrup, wt. 14.3 g (95%), which crystallized. After one recrystallization from a mixture of ethanol (6 ml/g) and water (10 ml/g), compound **2c** was obtained as colorless crystals (13.4 g); m.p. 76–77°, $[\alpha]_D^{25}$ −175.9° (*c* 1.0, ethanol); lit.[17] m.p. 76–77°, $[\alpha]_D^{18}$ −176.3° (*c* 0.8, ethanol). I.r. spectrum of **2c**: ν_{max}^{KBr} 2990, 2940, 2910, 1735 ($COCH_3$), 1460, 1448, 1380 and 1370 (doublet; CMe_2), 1305, 1240

($COCH_3$), 1220, 1190, 1160, 1140, 980, 920, 882, 854, 818 (CMe_2), and 742 cm^{-1}. G.l.c. analysis of **2c** showed only one peak, having a retention time of 154 sec. On t.l.c., it showed only one component, which had R_F 0.54 (solvent A), 0.93 (solvent B), and 0.82 (solvent C); these R_F values are very close to those found for **2d**.

Oxidation of 1,2:4,5-di-O-isopropylidene-β-D-fructopyranose (**2a**) *with methyl sulfoxide–acetic anhydride.* — To 52.1 g (200 mmoles) of **2a** were added methyl sulfoxide (142 ml, 2 moles) and acetic anhydride (186 ml, 2 moles). The resulting, colorless solution was kept, with exclusion of moisture, for 4 days at 25°, and then evaporated to a thin syrup at 60°/10 torr. Three 100-ml portions of toluene, followed by three 100-ml portions of methanol, were added and distilled off, and the thick syrup was freed of traces of solvents at 60°/0.1 torr, giving a partially crystalline mass,wt. 56.8 g. This was dissolved in 200 ml of chloroform; the solution was washed with six 20-ml portions of water, dried (anhydrous sodium sulfate), and evaporated to dryness, yielding a light-yellow, crystalline solid, wt. 56.2 g. T.l.c. showed that this material consisted solely of compounds **3** and **2d**.

To a solution of the mixture in absolute methanol (5 ml/g) was added water (2.5 ml/g), with swirling, giving a faintly cloudy solution which was nucleated with authentic **2d**. Crystallization of **2d** rapidly ensued; the suspension was kept for 2 h at 25°, for 2 h in a refrigerator, and overnight in a freezer. The colorless crystals of **2d** were filtered off (filtrate 1), washed with 25 ml of ice-cold 1:1 (v/v) methanol–water, and dried; wt. 27.6 g. On recrystallization from absolute methanol (2 ml/g) by the addition of water (1 ml/g), compound **2d** was obtained as prisms, wt. 26.3 g; m.p. 82.5–83°, $[\alpha]_D^{25}$ +26.1° (*c* 1.0, chloroform), +12.7° (*c* 1.0, acetone); lit.[14] m.p. 81–82.5°, $[\alpha]_D$ +26.8° (*c* 1.0, chloroform). I.r. data: ν_{max}^{KBr} 2995 and 2940 (both C–H), 2900, 1465, 1440, 1388 and 1376 (doublet, CMe_2), 1334, 1312, 1260, 1220, 1204, 1188, 1156, 1118, 1088 and 1074 (doublet), 1026, 1004, 986, 946, 924, 892, 862, 834, 816 (CMe_2), 782, 741, and 696 cm^{-1}. G.l.c. analysis of **2d** showed only one peak, having a retention time of 215 sec. T.l.c. analysis showed only one component, having R_F 0.79 (solvent A), 0.95 (solvent B), and 0.85 (solvent C); lit.[14] R_F 0.85 (solvent C). A mixture of compound **2d** with the acetate **2c** melted at 59°.

Filtrate 1 was evaporated to dryness, and the product was dried at 25°/0.1 torr over phosphorus pentaoxide, affording a crystalline mass, wt. 27.6 g. This was recrystallized from hexane (4 ml/g) to give **3** as elongated prisms, wt. 22.8 g, m.p. 102–103°; $[\alpha]_D^{25}$ −104.7° (*c* 1.0, acetone), −119.2° (*c* 1.1, chloroform), −113.5° (*c* 1.0, ethanol); lit.[12] m.p. 101–102°, $[\alpha]_D^{25}$ −100.4° (*c* 2.41, acetone); lit.[14] m.p. 101.5–102.5°, $[\alpha]_D^{20}$ −126.4° (*c* 1.0, chloroform); lit.[16] m.p. 99–101°, $[\alpha]_D$ −106° (*c* 0.26, ethanol). I.r. data: ν_{max}^{KBr} 3000, 2945, 2900, 1740 (C=O), 1460 (CH_2), 1390, 1383 and 1378 (doublet, CMe_2), 1318, 1292, 1235, 1170, 1105, 1074, 1026, 1012, 1000, 976, 894, 876, 860, 850, 806 (CMe_2), 792, and 762 cm^{-1}. G.l.c. analysis of **3** showed only one peak, having a retention time of 68 sec. T.l.c. analysis showed only one component, having R_F 0.56 (solvent A), 0.89 (solvent B), and 0.65 (solvent C); lit.[14] R_F 0.65 (solvent C); R_{2a} (solvent B) of **2c**, 1.24; **2d**, 1.26; **3**, 1.19; and **4a**, 0.86; lit.[12] R_{2a} (solvent B) of **2c** (or **2d**), 1.26; **3**, 1.18; and **4a**, 0.86.

Preparation of compound **3** *by oxidation of* **2a** *with ruthenium tetraoxide.*—The oxidation was conducted by the method of Jones *et al.*[18]. Compound **2a** (26 g, 100 mmoles) was dissolved in ethanol-free chloroform (155 ml); water (155 ml) was added, followed by anhydrous potassium carbonate (5.0 g; 36.2 mmoles) and potassium periodate (45 g; 195 mmoles), with vigorous magnetic stirring. Then 60.5% ruthenium dioxide powder (1.9 g; 8.6 mmoles) was added, and the mixture was stirred magnetically at room temperature. Ruthenium tetraoxide (yellow) formed in the reaction mixture. After 16 h, the tetraoxide had been completely reduced to the black dioxide, but t.l.c. of the mixture showed that the oxidation was not complete.

A further 5.0 g of potassium carbonate and 45 g of potassium periodate were added, and, 6 h thereafter, the oxidation was complete (as determined by t.l.c.). Isopropyl alcohol (5 ml) was then added (to reduce all of the ruthenium tetraoxide to dioxide), the suspension was filtered through Celite, and the two layers in the filtrate were separated. The aqueous phase was extracted with five 100-ml portions of chloroform, and the chloroform solutions were combined, washed once with water (10 ml), dried (anhydrous sodium sulfate), and evaporated to a colorless solid, wt. 25.3 g (98%). The product was recrystallized from petroleum ether (b.p. 30–60°; 500 ml) and ether (45 ml), to give a first crop of colorless crystals, wt. 23.6 g; m.p. 100–102°, $[\alpha]_D^{20}$ −119.2° (*c* 1.0, chloroform), $[\alpha]_D^{20}$ −104.7° (*c* 1.1, acetone). T.l.c. analysis showed only one component, having R_F 0.65 (solvent C). A second preparation yielded recrystallized material having m.p. 102–103° and $[\alpha]_D^{20}$ −119.6° (*c* 1.0, chloroform).

*Preparation of 1,2:4,5-di-*O*-isopropylidene-β-*D*-psicopyranose* (**4a**). — A solution of 12.9 g (50 mmoles) of diulose acetal **3** in absolute ethanol (500 ml) and water (200 ml) was stirred magnetically and kept below 5° in an ice bath while a suspension of 21.0 g (550 mmoles) of sodium borohydride in absolute ethanol (250 ml) was added dropwise during 30 min. The solution was stirred for 30 min after addition was complete, and then a 20-ml aliquot was removed and evaporated to dryness. G.l.c. analysis of a trimethylsilylated portion, under conditions which would have detected 0.1% of **2b**, showed only one peak, namely, that for **4b**, having a retention time of 111 sec. The product was isolated as described by James *et al.*[14], to give a colorless syrup which crystallized rapidly. This was dried for 24 h at 25°/0.2 torr over phosphorus pentaoxide, giving a mass of crystals, wt. 12.8 g. On recrystallization from pentane (15 ml/g), compound **4a** was obtained as rosettes of short needles, m.p. 68–69°, $[\alpha]_D^{25}$ −120.7° (*c* 1.0, chloroform), −118.9° (*c* 0.6, ethanol), −116.4° (*c* 0.7, acetone); lit.[12] m.p. 60–61°; lit.[14] m.p. 64–65°, $[\alpha]_D^{20}$ −126.8° (*c*. 1.0, chloroform); lit.[16] m.p. 62–64°, $[\alpha]_D$ −108° (*c* 1.5, ethanol). I.r. data: ν_{max}^{KBr} 3440 (OH), 2980, 2950, and 2930 (all C–H), 1465 (CH_2), 1390 and 1380 (doublet, CMe_2) 1320, 1272, 1260, 1238, 1220, 1212, 1172, 1110, 1060, 1019, 1008, 972, 875, and 859 (doublet), 814 (CMe_2), and 742 cm^{-1}. X-ray data: 2.25 (w), 2.31 (w), 2.52 (w), 2.80 (w), 2.85 (m), 2.90 (w), 2.95 (w), 3.40 (w), 3.50 (w), 3.60 (w), 3.80 (m), 4.25 (s), 4.70 (m), 4.85 (s), 5.06 (s), 5.26 (s), 5.42 (m), 5.75 (s), 7.70 (s), 8.60 (s), and 11.90 (s). T.l.c. analysis showed only one component, having R_F 0.23 (solvent A), 0.65 (solvent B), and 0.25

(solvent C); lit.[14] R_F 0.21 (solvent C). G.l.c. analysis of the trimethylsilyl ether **4b** gave the same, single peak as for the ether of the "crude" product.

On being kept at room temperature for several months, the m.p. changed to 56–58°, but no change in R_F values (solvents A, B, and C), i.r. spectrum (both of the solid and in chloroform solution, with solvent compensation), or optical rotation occurred. The positions of the peaks in the X-ray powder diffraction scan were unchanged, but some of the relative intensities differed from those for freshly prepared **4a**, as follows: 2.85 (w), 2.90 (m), and 5.42 (s). These X-ray diffraction data differ significantly from those for compound **8**, which gave peaks at 2.95 (w), 3.08 (w), 3.79 (w), 3.88 (m), 4.10 (w), 4.46 (s), 4.60 (s), 4.95 (w), 5.17 (s), 5.64 (m), 6.80 (m), 7.30 (m), and 9.10 (s). Also, the i.r. spectrum of stale **4a** was quite different from that of **8**. Absence of hydrate formation on prolonged storage of **4a** was indicated by its elemental analysis after storage for 4 months.

Anal. Calc. for $C_{12}H_{20}O_6 \cdot 0.25\ H_2O$: C, 54.4; H, 7.8. Calc. for $C_{12}H_{20}O_6$: C, 55.4; H, 7.7. Found: C, 55.0; H, 7.6.

D-*Psicose* (**5a**). — A solution of diacetal **4a** (1.040 g, 4 mmoles) in 100 mM aqueous oxalic acid (100 ml) was heated for 4 h at 65°. The solution was cooled to room temperature, 2.2 g (11 mmoles) of finely powdered, anhydrous calcium carbonate was added slowly, with stirring, and the suspension was then stirred for 1 h, and filtered. The solids were washed with water (10 ml), and the filtrate and washings were combined, and evaporated to a syrup which was dried for 24 h at 25°/0.2 torr over phosphorus pentaoxide; final wt., 706 mg (98%), $[\alpha]_D^{25}$ +4.7° (*c* 1.0, water); lit.[8] $[\alpha]_D^{25}$ + 4.7° (in water). G.l.c. analysis of the per(trimethylsilyl) derivative **5b** (prepared as for **1b**) showed only one peak, having a retention time of 294 sec. T.l.c. with 3:6:8:3 (v/v) formic acid–butanone–*tert*-butyl alcohol–water, on plates precoated with microcrystalline cellulose, showed only one component, having R_F 0.38; in this system, D-fructose has R_F 0.28.

2,3:4,5-Di-O-isopropylidene-β-D-fructopyranose (**6a***). — Compound **6a** was prepared from **1a** by an improved method[3]. Recrystallized from 1:1 (v/v) ether–pentane (10 ml/g), it had m.p. 97°, $[\alpha]_D^{25}$ −38.1° (*c* 1.0, acetone), and i.r. spectrum identical with that of the authentic compound[23]. G.l.c. analysis of its 1-(trimethylsilyl) ether (**6b**) showed only one peak, having a retention time of 114 sec. T.l.c. analysis showed R_F 0.31 (solvent A), 0.71 (solvent B), and 0.27 (solvent C).

Oxidation of 2,3:4,5-di-O-isopropylidene-β-D-fructopyranose (**6a**) *with methyl sulfoxide–acetic anhydride.* — To 3.0 g (11.6 mmoles) of compound **6a** were added methyl sulfoxide (8.0 ml; 112 mmoles) and acetic anhydride (10.0 ml; 107 mmoles). The resulting, colorless solution was kept, with exclusion of moisture, for 4 days at 25°. The pale-yellow solution was diluted with 300 ml of chloroform, washed successively with four 150-ml portions of water, four 150-ml portions of saturated, aqueous sodium hydrogen carbonate solution, and two 150-ml portions of water, dried (anhydrous sodium sulfate), and evaporated to a pale-yellow syrup (wt. 3.1 g). T.l.c. (solvent

*The S_4^6 conformation depicted was found by Maeda and co-workers[24].

C) revealed the presence of two zones (R_F 0.72 and 0.39). A solution of this syrup (2.0 g) in 4.0 ml of acetone was applied in a streak (4–6 mm wide) to four preparative, thin-layer plates (18 cm × 20 cm × 600 μm, 20 g of adsorbent per plate), which were then developed with the aforementioned solvent. Zones were detected by the technique of Horton and Tsuchiya[25], and were seraped from the plates without great regard for high recovery (in order to obtain each compound pure). For each plate, two zones were thus obtained; similar zones were combined, and the compounds were separated from the adsorbent by extraction with acetone.

In this way, a sulfur-containing syrup (0.7 g) was obtained; R_F 0.72 (solvent C) and $[\alpha]_D^{25}$ −54.6° (*c* 0.7, chloroform). G.l.c. analysis of the syrup showed only one peak, having a retention time of 198 sec, as compared with 197 sec for an authentic sample of **6c**. However, the results of elemental analysis suggested that the syrup was a mixture of **6c** and **6d**, a conclusion confirmed by the i.r. spectrum; ν_{max}^{film} 2990 and 2940 (both C–H), 1710 (C=O), 1455 (CH_2), 1385 and 1376 (doublet, CMe_2), 1320, 1310, 1258, 1210, 1188, 1170, 1112, 1078, 1028, 988, 918, 894, 874, 816 (CMe_2), 768, 746, and 695 cm^{-1}.

The second zone gave syrupy 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hexosulo-2,6-pyranose (**7**) (0.5 g); R_F 0.39 (solvent C); $[\alpha]_D^{25}$ −41.2° (*c* 0.8, chloroform); ν_{max}^{film} 2995 and 2940 (both C–H), 2740 (aldehyde CH), 1745 (C=O), 1455 (CH_2), 1380 and 1370 (doublet, CMe_2), 1320, 1255, 1215, 1168, 1112, 1060, 1020, 988, 892, 814 (CMe_2), and 768 cm^{-1}. G.l.c. analysis of **7** showed only one peak, having a retention time of 59 sec.

Anal. Calc. for $C_{12}H_{18}O_6$: C, 55.8; H, 7.0. Found: C, 55.8; H, 7.2.

In a repetition of the oxidation, followed by attempted distillation of **7**, it was found that the aldehyde group in **7** is readily susceptible to oxidation when **7** is heated in air. A preliminary separation of **7** from the mixture of **6c** and **6d** was achieved by partition of the reaction product between equal volumes of hexane and water. By t.l.c., it was found that most of **7** was present in the aqueous layer, whereas the other products were in the hexane layer. Evaporation of the hexane layer gave a colorless, slightly viscous syrup, b.p. 106–112°/0.08 torr, n_D^{25} 1.4762, having an elemental analysis indicating that it was a mixture of **6c** and **6d**; it was not further investigated. Evaporation of the aqueous layer gave almost pure **7** as a colorless syrup. On distillation, with a very fine capillary bleeding air, it gave a colorless, very viscous syrup, b.p. 108–111°/0.07 torr; n_D^{25} 1.4668; R_F 0.52 (solvent C); $[\alpha]_D^{22}$ −46.5° (*c* 1.3, acetone); ν_{max}^{film} 3300 (broad, OH of COOH), 2990 and 2940 (CH), 2640 (broad, OH of COOH), 1740 (C=O), 1450 (CH_2), 1380 and 1370 (doublet, CMe_2), 1344, 1308, 1250, 1220, 1170, 1100, 1040, 1005, 932, 892, 810 (CMe_2), 775, 720, and 690 cm^{-1}. G.l.c. analysis of the compound showed only one peak, having a retention time of 289 sec. The compound gave an acidic solution on being dissolved in water, and its elemental analysis agreed with that calculated for 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hexulopyran-1-onic acid.

Anal. Calc. for $C_{12}H_{18}O_7$: C, 52.5; H, 6.6. Found: C, 52.2; H, 6.9.

*Reduction of 2,3:4,5-di-*O*-isopropylidene-β-*D*-arabino-hexosulo-2,6-pyranose* (**7**). — A solution of 429 mg (1.9 mmoles) of acetal **7** in absolute ethanol (38 ml) and water 16 ml) was stirred magnetically and kept below 5° in an ice-bath while a suspension of 1.6 g (42 mmoles) of sodium borohydride in absolute ethanol (20 ml) was added dropwise during 30 min. The mixture was stirred for 30 min after addition was complete, and then diluted with 100 ml of saturated, aqueous sodium chloride solution; the resulting solution was extracted with four 25-ml portions of dichloromethane. The extracts were combined, washed with three 20-ml portions of water, dried (anhydrous sodium sulfate), and evaporated to a colorless syrup which crystallized rapidly. The mass was dried for 24 h at 25°/0.2 torr over phosphorus pentaoxide, giving crystals, wt. 389 mg (91%). Recrystallization, by dissolving in boiling ether (2 ml), cooling, and adding pentane (2 ml), gave compound **6a** as rosettes of needles, m.p. 97°, $[\alpha]_D^{25}$ −38.1° (*c* 1.5, acetone); lit.[3] m.p. 97°, $[\alpha]_D^{25}$ −38.1° (*c* 1.7, acetone); the i.r. spectrum agreed with the published spectrum[23].

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